Applicants followed that suggestion, canceled the existing claims 1-23 in the application and replaced them with claims 33-52. The replacement claims 33-52 correspond substantially to replaced claims 1-23 as set forth below. Some amendments were made in claims 24, 29, 32 and 34-52 in addition to claim 33, which has been amended as detailed below in accordance with discussion at the personal interview.

Cancelled Claims	Replacement Claims
1	33
2	cancelled
3	34
4	35
5	36
6	37
7	38
8	cancelled (incorporated into claim 38)
9	cancelled (incorporated into claim 33)
10	39
11	40
12	41
13	42
14	43
15	44
16	45
17	46
18	47
19	48
20	49
21	50
22	51
23	52

Applicants added a new claim 53, support therefor being found in the specification as a whole, *e.g.*, pages 8 and 9. Applicants also cancelled the former claims 2, 8 and 9 (the latter two claims now being substantially incorporated into claims 38 and 39, respectively). Applicants request that in all future proceedings, claims 24-53 be examined in the application.

II. INTERVIEWS

A. Personal Interview

Applicants express their appreciation to Examiners Michael Miller and David Naff for the courtesy of granting a personal interview to the undersigned counsel on December 19, 2001.

A short summary of the interview appears in the "Interview Summary" issued on December 19. Applicants wish to expand on the summary in accordance with MPEP § 713.04.

1. Rejections of Claims 1-34 (*sic.*, 32) Under 35 U.S.C. § 112, First Paragraph

Applicants argued that the rejection of Claim 1 under this section of the statute is misplaced based on the court decisions of *In re Johnson*, 558 Fed.2d 1008, 1019, 194 U.S.P.Q. 187, 196 (CCPA 1977) and *Ex parte Grasselli*, 231 U.S.P.Q. 393 (Bd. App. 1983), aff'd mem., 738 Fed.2d 453 (Fed. Cir. 1984). The Examiners said that they would consider arguments based on these decisions if Applicants submit them in a response to the Office Action.

Alternatively, the Examiners said that this rejection would be overcome if Applicants incorporate the subject matter of Claim 9 into Claim 1 and delete from Claim 1 the recitation of "other than galactose".

With respect to Claim 34 (*sic.*, 32), Applicants argued that support exists for the disputed recitation ("a compound which is capable of being converted into the substrate for the galactose oxidase") in the specification as a whole, for example, in the original Claim 1. The Examiners asked Applicants to submit appropriate arguments in a response.

2. Rejections of Claims 4, 8-11 and 17-23 Under 35 U.S.C. § 112, Second Paragraph

These rejections were caused by the Examiner reviewing the original claims of the PCT application, rather than the "new claims", filed during the international stage in August of 1999. Applicants pointed out that the "new claims" should have been examined since it was Applicants' understanding that they were communicated by the International Bureau to the U.S. Patent and Trademark Office ("PTO") and Applicants filed on January 18, 2000 a Request to Examine Application on the Basis of the Text Amended Under Article 34 of PCT, bringing that matter to the PTO's attention. Nonetheless, the Examiners suggested that the easiest way to fix this problem would be to cancel all the existing claims and insert a replacement set of claims which would include the August 1999 claims.

3. Rejection Under 35 U.S.C. § 102 Over *van der Lugt et al.*

Applicants pointed out that this reference was improperly cited under 35 U.S.C. § 102(b) because it was published less than one year from Applicants' earliest U.S. priority date of July 22, 1997 (based on U.S. provisional application No. 60/053,451). The Examiners agreed, but said the reference would still be citable under 35 U.S.C. § 102(a). They suggested that if Applicants wanted to remove that reference as prior art, it could be done by swearing behind its publication date of 1997 in a Declaration Under 37 CFR § 1.131 ("Section 131").

Alternatively, the Examiners suggested that the amendment of Claim 1 by incorporating into it Claim 9 would also overcome this rejection, providing that the disclosure in *van der Lugt et. al.* of the use of galactose oxidase in a dough containing stachyose would not anticipate the definition of the substrate compound of Claim 9 (a galactan, a galactose oligomer or a galactose dimer). In this connection, Applicants

note that the "Interview Summary" contains a typographical error. The word "not" is missing in the last line of comments after the word "does". Applicants understand this line to read "...rejection providing stachyose does not read on claim 9." If that understanding is incorrect, Applicants would appreciate the Examiner's comments on this issue.

4. Rejections Under 35 U.S.C. § 103

The Examiners pointed to the disclosure in Clark (U.S. Patent 4,458,686) of D-galactose, stachyose and lactose as typical substrates for galactose oxidase. They asked Applicants to establish that this disclosure would not have an adverse effect on patentability of claim 1 amended to include the Markush group of the substrates of claim 9 (or claim 1 in its present form). In particular, they expressed their belief that lactose is a galactose dimer.

If Applicants can establish the lack of such adverse effect by Clark, the Examiners appeared to indicate that evidence of unexpected results present in the application is likely to overcome these rejections. They suggested that Applicants strongly argue such evidence. With respect to that evidence in Example 2, the Examiners asked Applicants to confirm that arabinogalactan treated with arabinofuranosidase to cleave arabinose is the same as galactan.

B. Telephone Interviews

Applicants also wish to express their appreciation to Examiner Meller for granting three telephone interviews, on March 1, 7 and 27, 2002.

On March 1, the undersigned Counsel inquired about the reasons for the indication in the Advisory Action that claim 40 (now claim 39) raised new issues and

new matter. Mr. Meller said it raised those issues because there is no support in the specification for the combination of lactose and galactose.

In the March 19th interview, Applicants discussed with the Examiner claims 33 and 40, and Declaration Under 37 C.F.R. § 1.131 ("131 Declaration").

(i) CLAIMS 33 AND 40

Mr. Meller said he would withdraw the new matter and new issue objections to claim 33 if, in section (ii) "including at least one" is changed to "which is at least one."

He also said that if Applicants identify support in the specification for the combination of lactose and galactose recited in claim 40, he would withdraw the new matter rejection, but not the new issue rejection.

(ii) DECLARATION UNDER 37 CFR §1.131

Mr. Meller explained that his reason for indicating that the December 1996 conference in the Netherlands was prior art and therefore the inventors must establish that they completed their invention prior to that date, is the presence of the word "activity" in 37 C.F.R. § 1.131. He also said that roles of all of the inventors in making the invention must be explained (as required by section 715.04 of the Manual of Patent Examining Procedure ("MPEP")). According to Mr. Meller, the report included with the Declaration Under 37 C.F.R. § 1.131 ("131 Declaration"), executed on January 24, 2002, did not specify the role played by Messrs. Rouau and Søe. Finally, Mr. Meller said that there appears to be a discrepancy between the dates in the Declaration and the report, insofar as the inventors in the Declaration stated that their invention was completed prior to 1997, while the report indicates that the research was conducted in the time period 1995-1998. Applicants' Counsel pointed out to the Examiner that Applicants made a sworn statement in the Declaration that their invention was

completed prior to 1997. He acknowledged it, but said that the discrepancy needs to be explained.

Applicants' Counsel also asked Mr. Meller for his basis for insisting in the Advisory Action that Applicants must establish that lactose was part of their invention made prior to the date of the reference, since they already established the reduction to practice of at least one species of their invention, which is sufficient to swear behind a reference under 37 C.F.R. § 1.131 (sections 715.02-715.03 of the MPEP). Mr. Meller said that he felt it is important because Applicants alleged some criticality in the use of lactose, but, according to him, Applicants can argue that the evidence of making the invention prior to the date of the reference need not include lactose.

In the March 27th interview, Counsel asked Mr. Meller if he would consider and enter into the record a second Amendment Under 37 C.F.R. § 1.116 and a Supplemental Declaration Under 37 C.F.R. § 1.131. Mr. Meller advised that he was not likely to enter a second Amendment Under 37 C.F.R. § 1.116, nor a Supplemental Declaration Under 37 C.F.R. § 1.131 in this application because the final office action had been issued, Applicants responded and he replied to the response in the Advisory Action.

III. CLAIMS 1-34 (*sic*, 32) SATISFIED REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH. AMENDED CLAIMS CONTINUE TO SATISFY THAT REQUIREMENT.

Claims 1-32 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to a person skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, it was alleged that Applicants' insertion of "other than galactose" in claim 1 raised the issue of new matter.

As discussed during the interview, CCPA and other court decisions provide support for Applicants' assertion that the deletion of one of several species expressly recited in the specification is proper and does not constitute new matter. *See In re Johnson, supra.* Since Applicants described galactose as one of several substrates for galactose oxidase (*e.g., see* page 8, lines 16-20), they possessed the subject matter of the invention of claim 1 prior to this Amendment, when their application was filed.

Nonetheless, Applicants amended claim 1 (now claim 33) to incorporate the limitations of claim 9, as also suggested by the Examiners. The amended claim continues to satisfy the requirements of Section 112.

Claim 32 was also rejected under the same section of the statute, because, allegedly, it lacked support for "a compound which is capable of being converted into the substrate for the galactose oxidase". Applicants also respectfully traverse this rejection. In addition to support for this limitation in the originally-filed claim 1, support for this limitation is present in the specification, considered as a whole (*e.g., see* page 8, line 24 - page 9, line 9).

IV. CLAIMS 33 AND 39

Applicants respectfully submit that claims 33 and 40, respectively, submitted in the Amendment Under 37 C.F.R. § 1.116, did not raise new issues or issues of new matter.

In claim 33 the recitation of "at least one" was substantively and substantially the same as in: claim 9 of Applicants' Amendment Under 37 C.F.R. § 1.111 filed on May 31, 2001 in which the oxidizable substrate compound was defined as comprising "a galactan, a galactose oligomer or a galactose dimmer"; and, in claim 1, in the same Amendment, which defined the second component as the oxidizable substrate "and/or

an enzyme." These limitations are supported by the specification, considered as a whole, *e.g.*, at pages 5 and 8.

The recitation of "a combination of lactose and galactose" in claim 40 is also supported in the specification considered as a whole, *e.g.*, at pages 7 and 8.

Nonetheless, in the interest of expediting prosecution, Applicants amended the aforementioned claims (now claims 33 and 39) as suggested by the Examiner. The amended claims continue to be supported by the specification.

V. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH.

Claims 4, 8-11, 17, and 23 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for a number of reasons. As agreed with the Examiners during the personal interview, these rejections occurred because the Examiner apparently was reviewing original claims filed in the international stage of the PCT application on June 4, 1996, rather than the new claims filed in August 1999. Applicants' cancellation of claims 1-23, and the introduction of the replacement claims 33-52, overcomes that rejection.

VI. CLAIMS REJECTED UNDER 35 U.S.C. § 102(b) OVER van der LUGT ET AL. ARE PATENTABLE IN VIEW OF THE DECLARATION UNDER 37 C.F.R. § 1.131 AND SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.131, FILED HEREWITH.

Claims 1, 4, 8, 13-16, 19, 21 and 23 (now claims 33, 35, 38, 42-45, 48, 50 and 52, respectively) were rejected as anticipated by van der Lugt et al., "Application of Oxidoreductases in Baking: Impact on Gluten Structure and Dough Rheology," Eur. Symp. Enzymes Grain Process., proc. 1st (1997), Meeting Date 1996 in The Netherlands (van der Lugt). This rejection is overcome, at least because the enclosed Declaration Under 37 C.F.R. § 1.131 (which is a copy of the Declaration filed on February 11, 2002) and Supplemental Declaration Under 37 C.F.R. § 1.131

("Supplemental 131 Declaration") establish that Applicants made their invention in a WTO country prior to the effective date of the reference. In this respect, Applicants wish to reiterate that the effective date of the reference is 1997, its publication date, rather than the December 2-4, 1996 meeting date in The Netherlands. Applicants are also enclosing an unexecuted version of the Supplemental 131 Declaration to expedite prosecution of the application. Applicants will provide an executed version of that Supplemental Declaration once their Counsel receives it.

Applicants note the Examiner's indication that the effective date of van der Lugt is the date of the meeting in The Netherlands, i.e., December 2, 1996. This indication was based on the presence of the term "activity" in 37 C.F.R. § 1.131 ("Section 131). Applicants respectfully submit that this term is used to enable Applicants to overcome a rejection of their claims, with a declaration provided for in Section 131, in view of a public knowledge or use of the invention" ... in this country." 35 U.S.C. § 102(a)[1] ("Section 102(a)"). This is underscored by the MPEP, Section 715, which states, in relevant part:

> An applicant may make an admission, or submit evidence of use of the invention or knowledge of the invention by others, or the examiner may have personal knowledge that the invention was used or known by others in this country. See MPEP § 706.02(c) and § 2133.03. The effective date of the

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[1] This section of the statute states, in pertinent part:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent,...

While the word "public" is not present in the paragraph cited above, the courts have held that knowledge or use in this country must be public to qualify as prior art under Section 102(a). *See* Carella v. Starlight Archery & Pro Line Co., 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

> activity used to reject the claim(s) is the date the activity was first known to have occurred.

Page 700-202 of the MPEP.

It is well-established that substantially all categories of prior art are found in Section 102 of the Patent Statute. There is simply no other provision of Section 102 which might define a meeting in The Netherlands as prior art. For example:

> Section 102(b) defines prior art which is a patent or a printed publication;
>
> Section 102(d) defines prior art which is a patent obtained by the applicant, his legal representatives or assigns in a foreign country, under certain conditions;
>
> Section 102(e) defines prior art which is an invention patented on an application for patent by another filed in the United States prior to the invention thereof by the Applicant (or an international application by another who has fulfilled some specified requirements of § 371(c)), or an invention described in a published U.S. patent application by another (which satisfies substantially the same criteria as the patent granted to another, described above); and
>
> Section 102(g) defines prior art which is an invention made in this country by another inventor prior to an applicant's invention thereof, and such other inventor did not abandon, suppress or conceal it.

Thus, a meeting in The Netherlands is not an "activity" which can be used to reject Applicants' claims as of the date of that meeting.

Van der Lugt has the publication date of 1997; therefore, van der Lugt, as prior art, has the effective date as of its publication date, i.e., 1997. Since Applicants established in their 131 Declaration that at least one, and in fact several, species of the invention included in claim 33 were reduced to practice prior to 1997, they have

established that their invention was made prior to the 1997 effective date of van der Lugt.[2]

Applicants also wish to address other reasons set forth by the Examiner for the proposition that the 131 Declaration did not place the application in condition for allowance.

1. Applicant has not established exactly when the experimentation in the declaration under 37 C.F.R. § 1.131 was conducted (other than prior to 1997).

Applicants respectfully submit that it is well-established that a Section 131 declaration need not identify the date the invention was made; Applicants only need to allege that the acts referred to in the declaration occurred prior to a specified date, i.e., the effective date of the reference. *See* § 715.07 of the MPEP (August 2001, page 700-10). Thus, a sworn statement by Applicants that their invention was made in the World Trade Organization country prior to the effective date of van der Lugt is sufficient under the established practice involving Section 131.

2. Applicants did not establish that lactose was ever tested.

It is also well-established that a Section 131 declaration presents a showing sufficient to establish a date of claimed invention prior to the effective date of the reference if the declaration shows that at least one species of the claimed invention was made prior to the effective date of the reference. See § 715.02 of the MPEP (August 2001, page 700-05). As discussed above, Applicants' 131 Declaration establishes that

[2] While in the 131 Declaration, Applicants cite claim 33 as it existed in the Amendment Under 37 C.F.R. § 1.116, the amended claim 33 (included herein) is substantively the same in view of the work described in the 131 Declaration. This is evidenced by the fact that all of the species described by Applicants in the 131 Declaration as having been made prior to 1997 are also covered by the herein amended claim 33. *Also see* the Supplemental 131 Declaration which includes as Exhibit 1 claim 33 as amended in this Preliminary Amendment.

several species of their invention were made prior to 1997, thereby satisfying the requirements for a Section 131 declaration.

3. Alleged discrepancy between the dates in the Declaration and the report (Exhibit B).

While Exhibit B indicates that it covers the research program from 1995 to 1998, Applicants made a sworn statement in the 131 Declaration that their invention was made prior to 1997. As explained in the Supplemental Declaration, the work related to the invention was performed by the inventors prior to 1997. The report merely corroborates Applicants' statement that their invention was made and Applicants' sworn statement establishes that it was made prior to the 1997 effective date of van der Lugt.

4. The contribution of Xavier Rouau and Jorn Børch Søe.

Applicants were also required by the Examiner to explain the roles of all of the inventors because the report did not specify the role played by Messrs. Rouau and Søe.

In the Supplemental 131 Declaration, Applicants explained that they collaborated with each other in the work pertaining to the invention, and that all three of them contributed to the effort described in the 131 Declaration. This is underscored by the indication on the cover of the report that the work was carried out under the supervision of Mr. Xavier Rouau.

For all the reasons discussed above, van der Lugt is not prior art to Applicants' invention.

VII. CLAIMS 1-32 (NOW 33-52) AND 24-32 ARE PATENTABLE IN VIEW OF SOMERS, WO, BANKS AND CLARK AT LEAST BECAUSE THE COMBINATION OF THE REFERENCES IS ERRONEOUS AS A MATTER OF LAW. EVEN THE IMPROPER COMBINATION WOULD NOT HAVE RENDERED APPLICANTS' CLAIMS OBVIOUS.

Claims 33-52 were rejected as unpatentable over Somers et al., Cereal Food World, July 1996, volume 41, number 7 ("Somers") or van der Lugt, in view of WO

96/39851 ("WO"), Banks et al., U.S. Patent 4,828,853 ("Banks") and Clark, Jr., U.S. Patent 4,458,686 ("Clark"). It was alleged that Applicants had misstated the teachings of Clark in the previous Amendment, insofar as Clark teaches the equivalency of galactose and lactose as substrates for galactose oxidase. In response to Applicants' arguments that the references were not properly combinable, it was stated that the references cited by the Examiner established knowledge in the art. For example, it was stated, that WO shows the addition of hemicellulases, cellulase, etc., that can be added to dough to improve its properties.

Applicants' reliance on unexpected results shown in the Application was rejected, because, allegedly, they are irrelevant to the art cited by the Examiner in the rejection since Applicants did not show directly unexpected results compared to the art of record. Office Action, pages 4-5.

Applicants respectfully disagree with allegations in the Office Action, and respectfully request reconsideration of this rejection in view of the removal of the van der Lugt reference as prior art, and the following remarks.

Initially, Applicants reiterate their assertion that the combination of the remaining references, WO, Somers, Banks, and Clark is erroneous as a matter of law. Applicants' argument supporting that assertion was set forth in detail in the Amendment Under 37 C.F.R. § 1.111 filed on May 31, 2001, incorporated herein by reference. In particular, Applicants were not provided with any factual basis for the assertion that the teachings of the various references should be combined to modify Somers' teachings with selectively-isolated portions of the disclosures of WO, Banks and Clark. It is well-settled that the PTO has the burden to establish, based on prior art, a motivation to combine

the references. This has not been done in the Office Action. Instead, it was simply stated that the references cited in the Office Action established what is known in the art.

While Applicants agree that the references, individually, establish the knowledge in the art of various aspects of similar technology, such knowledge alone is not sufficient to provide motivation to combine the references and modify them as was done in the Office Action of January 31, 2001 ("First Office Action") (apparently included implicitly in the August 9, 2001, Office Action ("Second Office Action")).

Applicants wish to briefly discuss the references relied upon in the rejection. Somers teaches the use of galactose oxidase in the presence of galactose in a dough, and states that the use of galactose oxidase in the presence of galactose provides less pronounced results than that of glucose oxidase. Applicants agree that WO teaches a method of improving the rheological properties of a flour dough by adding an oxidoreductase capable of oxidizing maltose, such as hexose oxidase, and, in one embodiment, at least one additional enzyme, such as a cellulase, a hemicellulase, a xylanese, a glucose oxidase, a lipase and a protease. (WO, page 16).

Banks teaches the presence of a large number (at least 16) of sugars, in baked products. Two of such sugars are lactose or galactose. Clark teaches that D-galactose, stachyose or lactose can be used as substrates for galactose oxidase (*see* table at columns 7-8).

Nonetheless, any possible, albeit improper combination of Somers, WO, Banks and Clark would not have suggested to a person of ordinary skill in the art Applicants' invention of claims 24, 33 or 38, and claims dependent therefrom. Such an improper combination would have comprised a composition containing galactose oxidase, and dough which contains galactose, hexose oxidase, specifically taught in WO, as well as

several other enzymes taught in WO, sugars, such as lactose or galactose. Such an improper, and artificially-created composition would not have suggested to a person of ordinary skill in the art the composition now recited in claims 24, 33 or 38, *e.g.*, a composition comprising a galactose oxidase (as a first component) and (as a second component) at least one of the recited oxidizable substrates for the galactose oxidase (including a galactan, a galactose oligomer or a galactose dimer or a compound naturally naturally present in cereal flour or a hydrolysis product of arabinogalactan), and an enzyme which is capable of converting a compound into a substrate for the galactose oxidase. Of course, claims 24, 33 and 38 also include the combination of oxidizable substrates for the galactose oxidase, as recited therein which would not have been suggested by the artificially-created composition.

None of the references, nor the improper and artificially-made combination of the references, suggests Applicants' claimed composition. For example, the references do not suggest the claimed oxidizable substrate for the galactose oxidase, including a galactan, a galactose oligomer or a galactose dimer. In this connection, Somers' galactose, and D-galactose of Clark are monomeric galactoses which would not have rendered obvious Applicants' claimed invention.

Furthermore, in response to the Examiner's inquiry during the interview, Applicants wish to point out that lactose is a dimer of D-glucose and D-galactose (see the attached page 843 of the Merck Index (1989) teaching that hydrolysis of lactose with acid produces one mole of D-glucose and one mole of D-galactose).

With respect to stachyose , it appears to include two molecules of galactose (see the attached page from Plant Biology Index and page 678 from Merck Index). However, it is not a galactose dimer nor a galactose oligomer since it includes at least one

additional molecule of sugar. In contrast, as is known to those skilled in the art, the terms "galactose dimer" or "galactose oligomer" refer to sugars containing only galactose units.

Even if, arguendo, the improper combination of references did establish a *prima facie* case of obviousness, Applicants respectfully submit it would be effectively rebutted by evidence of unexpected results included in the application (as discussed at the interview). As shown in the specification, Applicants tested monomeric galactose as a substrate for galactose oxidase in comparison with di-galactose and arabinogalactan treated with arabinofuranosidase (which is believed to include a poly-galactose or oligomer of galactose (Example 2 and Fig. 4)). Applicants wish to confirm that an arabinogalactan treated with arabinofuranosidase to cleave arabinose is indeed galactan. As shown in the specification, it was surprisingly discovered by Applicants that galactan was approximately three times more effective as a substrate for galactose oxidase than galactose (i.e., monomeric galactose), and di-galactose was almost as good as galactan. This evidence of unexpected results provides strong support for Applicants' arguments that the art of record, taken alone or in any possible combination, fails to establish a *prima facie* case of obviousness of Applicants' claimed invention. The effect of galactose oxidase in reducing the undesirable side effects on the dough quality by the addition of hemicellulases was completely unknown in the art at the time that Applicants made their invention. This is established by a lack of any suggestion in the art to use galactose oxidase in the context of Applicants' claimed invention, and further underscored by the unexpected results which establish the inferiority of the use of monomeric galactose (disclosed in the prior art of record) as a substrate for galactose oxidase, as compared to di-galactose and galactan.

For all of the above reasons, withdrawal of this rejection is solicited.

VIII. CLAIMS 24-53 ARE PATENTABLE OVER SOMERS IN VIEW OF '94, BANKS, CLARK, GILLMORE AND YOKOTSUKA BECAUSE THE COMBINATION OF THE REFERENCES IS IMPROPER. EVEN THE IMPROPER COMBINATION WOULD NOT HAVE RENDERED THE CLAIMS OBVIOUS. EVIDENCE OF UNEXPECTED RESULTS REBUTS ANY POSSIBLE *PRIMA FACIE* OBVIOUSNESS.

Claims 1-34 (now 24-53) were rejected under 35 U.S.C. 103(a) as unpatentable over Somers or van der Lugt in view of WO 94/28728 ("'94"), Banks, Clark, Gillmore et al., U.S. patent 5,063,072 and Yokotsuka et al., U.S. patent 4,820,520, for reasons of record (presumably in the First Office Action) and for additional reasons stated in the Second Office Action. Those additional reasons include an allegation that Applicant had not provided any arguments except to state that the references were not properly combinable. It was also repeated that the references cited by the Examiner established knowledge in the art and Applicants had not provided any convincing arguments to address why the references were improperly combinable. It was alleged that the case of *prima facie* obviousness was satisfied because the references established that, at the time that the invention was made, the invention was obvious. Second Office Action, page 5.

Somers, Banks and Clark were discussed above. The disclosure of '94 was relied upon for its teaching of the addition of a laccase to a dough and bread products to improve their properties. It was also relied upon for its teachings that other enzymes may be used with laccase, such as cellulases, hemicellulases, pentosanases, glucose oxidase, lipase, protease and alpha-amylase. First Office Action, page 5.

Gillmore was cited for its apparent teaching that the alimentary paste and dough are the same and Yokotsuka for its disclosure that noodle dough is routinely used in dough making. First Office Action, page 6.

It was concluded that it would have been obvious to add hemicellulases in the composition of Somers since both Somers and '94 teach that the enzymes are used as dough improving agents and all enzymes are expected to improve dough. First Office Action, page 6. It was also stated that the use of noodle or alimentary dough would have been obvious in view of the teachings of Gillmore and Yokotsuka, and it would have been obvious to use lactose instead of galactose as a substrate for galactose oxidase in view of the teachings of Banks and Clark. First Office Action, page 6. It was additionally concluded that Clark's disclosure would have made it obvious to derive the galactose oxidase from a microorganism, such as a plant, fungi or bacteria. It was further asserted that it is well known in the art that microorganisms-derived enzymes have beneficial properties as compared to non- microorganisms derived enzymes. First Office Action, pages 6-7.

Applicants respectfully and strongly traverse this rejection.

Since van der Lugt has been removed as a prior art reference, it will not be discussed herein.

Applicants reiterate that while the references disclose what was known in prior art, Applicants were not presented with any reasons, based on this prior art, to indicate the motivation to combine selectively-isolated portions of teachings of prior art from the references with other selectively-isolated teachings to allegedly arrive at Applicants' claimed invention. Such a selective picking and choosing of various portions of the six references could only have been made with the improper hindsight provided by Applicants' own disclosure.

Such a combination would have failed to suggest Applicants' claimed composition, now recited, *e.g.*, in claim 33. The claimed composition includes, as the

first component, a galactose oxidase and as a second component, an oxidizable substrate for the galactose oxidase which comprises at least one of a galactan, a galactose oligomer or a galactose dimer, and further may comprise an enzyme which is capable of converting a compound into a substrate for the galactose oxidase. There is simply no disclosure in any of the individual six references or in the improperly created combination disclosure which would have suggested to a skilled person the claimed composition.

Similarly, there is no disclosure or suggestion in the six references of the subject matter of independent claims 24 and 38, i.e., a composition comprising, as a first component, a galactose oxidase (EC1.1.3.9) and, as a second component, an oxidizable substrate for the galactose oxidase, comprising at least one of a compound naturally present in cereal flour or a hydrolysis product of arabinogalactan.

Any possible case of *prima facie* obviousness would have been rebutted by the evidence of unexpected results, discussed in detail above, which compares the effect of galactose oxidase on galactan and galactose dimer to that on galactose. As discussed above, galactose under-performed the other two substrates (included in Applicants' claimed invention) approximately by a factor of three.

IX. REQUEST FOR ALLOWANCE

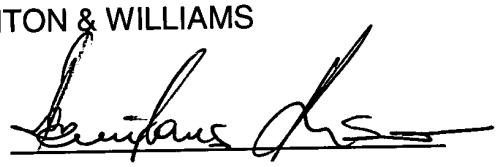
In view of the Declaration Under 37 C.F.R. § 1.131, the Supplemental Declaration Under 37 C.F.R. § 1.131 and arguments set forth above, an indication of allowance of all claims is solicited.

In the event that any outstanding issues remain, or the Examiner has any questions or suggestions for placing the application in condition for allowance, Applicants would appreciate the courtesy of a telephone call to the undersigned Counsel to resolve such issues and place the application in condition for allowance.

Respectfully submitted,

HUNTON & WILLIAMS

Dated: June 11, 2002

By: 

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APPENDIX A

Claims Entered in the Application as of February 20, 2002

1. A composition comprising, as a first component, a galactose oxidase (EC 1.1.3.9) and, as a second component, an oxidizable substrate for the galactose oxidase, other than galactose, and/or an enzyme which is capable of converting a compound into a substrate for the galactose oxidase.

2. A composition according to claim 1 wherein the second component oxidizable substrate is at least dimeric with respect to galactose.

3. A composition according to claim 1 or 2 wherein the galactose oxidase is derived from an organism which is selected from the group consisting of a plant species, a fungal species and a bacterial species.

4. A composition according to claim 1 wherein the compound which can be converted into a substrate for the galactose oxidase is a galactose containing compound.

5. A composition according to claim 1 wherein the compound which can be converted into a substrate for the galactose oxidase is a compound naturally present in cereal flour or a component hereof.

6. A composition according to claim 5 wherein the compound naturally present in cereal flour is a pentosan or a xylan.

7. A composition according to claim 1 which comprises a compound which is an oxidizable substrate for the galactose oxidase.

8. A composition according to claim 7 wherein said oxidizable substrate compound is a component of a compound naturally present in cereal flour.

9. A composition according to claim 8 wherein the oxidizable substrate compound comprises a galactan, a galactose oligomer or a galactose dimer.

10. A composition according to claim 9 wherein the oxidizable substrate compound is lactose.

11. A composition according to claim 1 wherein the second component is an enzyme selected from the group consisting of a hemicellulase, a pentosanase, a xylanase, an arabinofuranosidase, a mannanase, a galactanase and a ß-galactosidase.

12. A composition according to claim 1 which comprises a further enzyme component selected from the group consisting of a cellulase, a starch degrading enzyme, a lipase and a protease.

13. A composition according to any of claims 1, 2 or 4-12 further comprising a non-enzymic dough additive compound.

14. A composition according to claim 1 wherein the amount of galactose oxidase is in the range of 1 to 10,000 units per g.

15. A method of preparing a flour dough comprising adding to the dough an amount of the composition of any of claims 1, 2, 4-12 or 14 which is sufficient to obtain an amount of galactose oxidase activity in the dough which is in the range of 1 to 10,000 units per kg of flour.

16. A method according to claim 15 wherein the flour dough is a noodle dough.

17. A method according to claim 16, wherein the flour dough is an alimentary paste dough.

18. A method of preparing a bakery product, comprising baking the flour dough obtained by the method of claim 15.

19. A method of using the composition of claim 1, comprising adding the composition to dough ingredients, dough additives, a dough or a combination thereof.

20. A method according to claim 19, wherein the composition comprises a further enzyme component which includes a cellulase, a starch degrading enzyme, a lipase or a protease.

21. A method according to claim 19 or 20, wherein the composition further comprises a non-enzymic dough additive compound.

22. A method according to claim 19 or 20, wherein the galactose oxidase added to the dough ingredients, dough additives or the dough is substantially free of other enzyme activities.

23. A method according to claim 19, wherein the galactose oxidase is in the form of a crude enzyme preparation.

24. A composition according to claim 1, wherein the oxidizable substrate for the galactose oxidase comprises at least one of: a compound naturally present in cereal flour, lactose or a hydrolysis product of arabinogalactan.

25. A composition according to claim 24, wherein the compound naturally present in cereal flour includes non-starch polysaccharides comprising galactose moieties as structural elements.

26. A composition according to claim 24, wherein the compound naturally present in cereal flour includes hemicellulose compounds.

27. A composition according to claim 24, wherein the compound naturally present in cereal flour includes pentosans or xylans.

28. A composition according to claim 1, wherein the compound convertible into a substrate for the galactose oxidase includes at least one of a compound naturally present in cereal flour or a gum.

29. A composition according to claim 28, wherein the compound naturally present in cereal flour includes non-starch polysacchorides comprising galactose moieties as structural elements.

30. A composition according to claim 28, wherein the compound naturally present in cereal flour includes pentosans or xylans.

31. A composition according to claim 28, wherein the gum comprises guar gum or locust bean gum.

32. A composition according to claim 1 which further comprises, in the second component, a compound which is capable of being converted into the substrate for the galactose oxidase.

APPENDIX B

24. **(Once Amend d)** A composition ~~according to claim 1, wherein the~~**comprising, as a first component, a galactose oxidase (EC 1.1.3.9) and, as a second component, an** oxidizable substrate for the galactose oxidase **which** comprises at least one of: a compound naturally present in cereal flour, ~~lactose~~ or a hydrolysis product of arabinogalactan.

28. **(Once Amended)** A composition according to claim ~~1,~~**33,** wherein the compound convertible into a substrate for the galactose oxidase includes at least one of a compound naturally present in cereal flour or a gum.

29. **(Once Amended)** A composition according to claim 28, wherein the compound naturally present in cereal flour includes non-starch ~~polysaccharides~~**polysaccharides** comprising galactose moieties as structural elements.

32. **(Once Amended)** A composition according to claim ~~1~~**33** which further comprises~~, in the second component,~~ a compound which is capable of being converted into the substrate for the galactose oxidase.

~~1.~~ **33. (Twice Amended)** A composition comprising, as a first component, a galactose oxidase (EC 1.1.3.9) and, as a second component~~,~~**: (i)** an oxidizable substrate for the galactose oxidase **which is at least one of a galactan**, ~~other than~~**a** galactose **oligomer or a galactose dimer, (ii) an oxidizable substrate for the galactose oxidase which is at least one of a galactan, a galactose oligomer or a galactose dimer**, and~~/~~ **an enzyme which is capable of converting a compound into a substrate for th galactos oxidase,** or **(iii)** an enzyme which is capable of converting a compound into a substrate for the galactose oxidase.

~~3.~~**34. (Once Amend d)** A composition according to claim ~~1 or 2~~**33** wherein the galactose oxidase is derived from an organism which is selected from the group consisting of a plant species, a fungal species and a bacterial species.

~~4.~~**35. (Once Amended)** A composition according to claim ~~1~~**33,** wherein the compound which can be converted into a substrate for the galactose oxidase is a galactose containing compound.

~~5.~~**36. (Once Amended)** A composition according to claim ~~1~~**33** wherein the compound which can be converted into a substrate for the galactose oxidase is a compound naturally present in cereal flour or a component ~~hereof~~**thereof**.

~~6.~~**37. (Once Amended)** A composition according to claim ~~5~~**36** wherein the compound naturally present in cereal flour is a pentosan or a xylan.

~~7.~~**38. (Once Amended)** A composition ~~according to claim 1 which comprises~~ **comprising as a first component, a galactose oxidase (EC 1.1.3.9), and, as a second component:** a compound which is an oxidizable substrate for the galactose oxidase**, which is a compound naturally present in cereal flour**.

~~10.~~**39. (Once Amended)** A composition according to claim ~~9 wherein the oxidizable substrate compound is~~**38 further comprising** lactose **or galactose**.

~~11.~~**40. (Once Amended)** A composition according to claim ~~1~~**33** wherein the ~~second component is an~~ enzyme ~~selected from~~**which is capable of converting a compound into a substrate for** the ~~group consisting of~~**galactose oxidase includes** a hemicellulase, a pentosanase, a xylanase, an arabinofuranosidase, a mannanase, a galactanase ~~and~~**or** a ß-galactosidase.

~~12.~~41. **(Once Amended)** A composition according to claim ~~1~~33 which comprises a further enzyme component ~~selected from the group consisting of~~**including** a cellulase, a starch degrading enzyme, a lipase ~~and~~**or** a protease.

~~13.~~ 42. **(Twice Amended)** A composition according to any of claims ~~1,~~ ~~2~~33 or 4~~3~~5-~~12~~41 further comprising a non-enzymic dough additive compound.

~~14.~~ 43. **(Once Amended)** A composition according to claim ~~1~~33 wherein the amount of galactose oxidase is in the range of 1 to 10,000 units per g.

~~15.~~ 44. **(Twice Amended)** A method of preparing a flour dough comprising adding to the dough an amount of the composition of any of claims ~~1, 2, 4-12~~33 or ~~14~~35-41 which is sufficient to obtain an amount of galactose oxidase activity in the dough which is in the range of 1 to 10,000 units per kg of flour.

~~16.~~45. **(Once Amended)** A method according to claim ~~15~~44 wherein the flour dough is a noodle dough.

~~17.~~46. **(Once Amended)** A method according to claim ~~16,~~45 wherein the flour dough is an alimentary paste dough.

~~18.~~47. **(Once Amended)** A method of preparing a bakery product, comprising baking the flour dough obtained by the method of claim ~~15.~~44.

~~19.~~48. **(Once Amended)** A method of using the composition of claim ~~1,~~33, comprising adding the composition to dough ingredients, dough additives, a dough or a combination thereof.

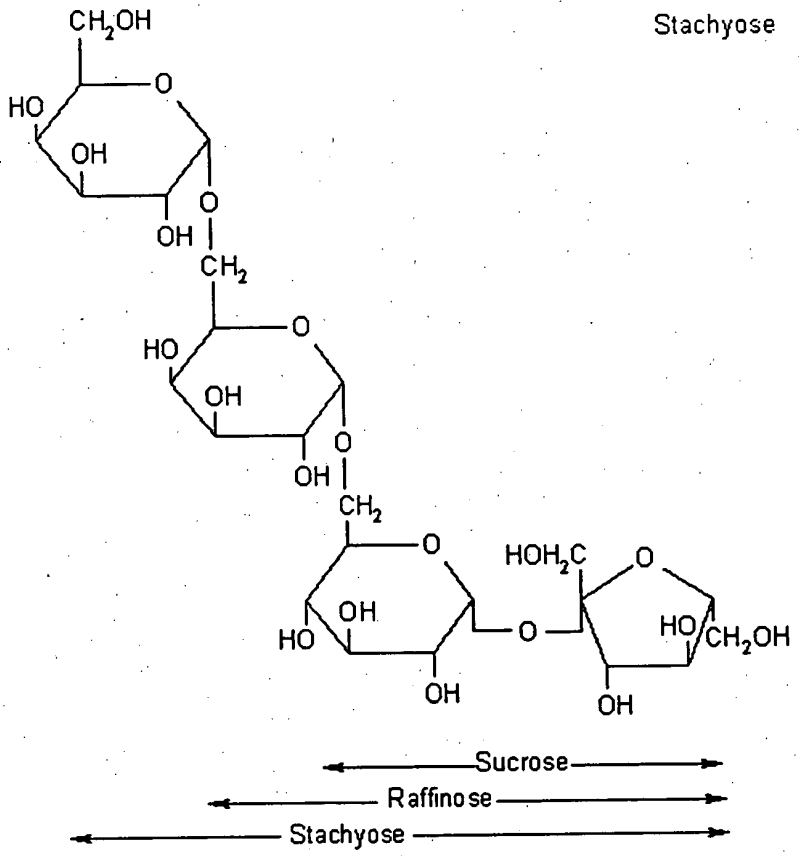
~~20.~~**49. (Onc Amended)** A method according to claim ~~19,~~**48,** wherein the composition comprises a further enzyme component which includes a cellulase, a starch degrading enzyme, a lipase or a protease.

~~21.~~**50. (Once Amended)** A method according to claim ~~19~~**48** or ~~20,~~**49,** wherein the composition further comprises a non-enzymic dough additive compound.

~~22.~~**51. (Once Amended)** A method according to claim ~~19~~**48** or ~~20,~~**49,** wherein the galactose oxidase **in the composition** added to the dough ingredients, dough additives or the dough is substantially free of other enzyme activities.

~~23.~~ **52.(Twice Amended)** A method according to claim ~~19,~~**48,** wherein the galactose oxidase is in the form of a crude enzyme preparation.

Stachyose



Stachyose, [*O*-α-D-galactopyranosyl-(1->6)-*O*-α-D-galactopyranosyl-(1->6)-α-D-glucopyranosyl-β-D-fructofuranoside], is a tetrasaccharide found coexists with raffinose and other related oligosaccharides in various organs of a number of plants. It is a major oligosaccharide in several plant species. Stachyose and other oligosaccharides of the raffinose family have been recognized as important transport carbohydrates in many woody plants, cucurbits, labiates, and legumes.

Stachyose synthesized in the leaves can be transported to other organs where it serves various functions. It can act as a storage carbohydrate in the storage organs such as roots and seeds. The accumulation of stachyose, along with sucrose and raffinsoe, in leaves can also provide frost-hardiness to winter-hardy plants.

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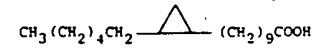
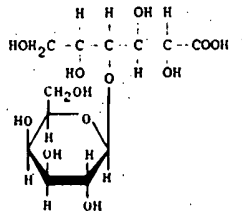


Crystals from acetone, mp 27.8-28.8°. Soluble in acetone, petr ether.

Methyl ester, $C_{20}H_{38}O_2$, liq, bp_3 187-187.5°. Soluble in many fat solvents.

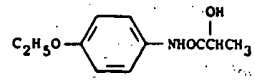
Amide. $C_{19}H_{37}NO$, *lactobacillamide.* Crystals, mp 79.4-81.5°. Soluble in dimethylformamide.

5219. Lactobionic Acid. *4-O-β-D-Galactopyranosyl-D-gluconic acid;* 4-(β-D-galactosido)-D-gluconic acid. $C_{12}H_{22}O_{12}$; mol wt 358.30. C 40.22%, H 6.19%, O 53.59%. Obtained by oxidation of lactose: Fischer, Meyer, *Ber.* **22**, 362 (1889); Ruff, Ollendorff, *ibid.* **33**, 1806 (1900); Isbell, *J. Res. NBS* **11**, 713 (1933); Margariello, U.S. pat. **2,746,916** (1956 to Nat. Dairy Res. Labs.); Eddy, *Nature* **181**, 904 (1958); Nishizuka *et al., J. Biol. Chem.* **235**, PC13 (1960). Manuf from lactose: Y. Sato *et al.*, Ger. pat. **2,038,230** (1971 to Hayashibara Co.), *C.A.* **74**, 142296c (1971). Crystal structure of calcium salt: W. J. Cook, C. E. Bugg, *Acta Crystallogr.* B29, 215 (1973). NMR studies: T. Taga *et al., Bull. Chem. Soc. Japan* **51**, 2278 (1978). For therapeutic use *see* Erythromycin Lactobionate.



Syrup. Freely sol in water, slightly sol in methanol, ethanol, glacial acetic acid. Dehydration by distillation with dioxane yields *lactobionic δ-lactone,* $C_{12}H_{20}O_{11}$, non-deliquescent crystals, dec 195-196°. Shows mutarotation. $[\alpha]_D^{20}$ +53.0° initial (c = 8.8) → $[\alpha]_D^{20}$ +22.6° final (240 minutes). Calcium salt, $C_{24}H_{42}CaO_{24}$, *calcium lactobionate.* Pentahydrate, hairlike needles in brushlike groups. When anhydr, slender needles from small amts of anhydr ethanol. $[\alpha]_D^{20}$ +23.7° (c = 6.28). n_D^{20} 1.4583 (concd syrup just before crystallization). Freely sol in water.

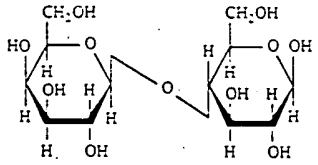
5220. *p*-Lactophenetide. *N-(4-Ethoxyphenyl)-2-hydroxypropanamide; p-lactophenetidide;* lactyl-*p*-phenetidin-*N*-(*p*-ethoxyphenyl)lactamide; Fenolactine; Lactophenin; Phenolactine. $C_{11}H_{15}NO_3$; mol wt 209.24. C 63.14%, H 7.23%, N 6.69%, O 22.94%. Prepn: Shapiro *et al., J. Am. Chem. Soc.* **81**, 6322 (1959).



Slightly bitter crystals from ethyl acetate + hexane, mp 117-118°. One gram dissolves in 330 ml cold, 55 ml boiling water, 8.5 ml alcohol; slightly sol in ether, petr ether.

THERAP CAT: Analgesic, antipyretic.

5221. Lactose. *4-O-β-D-Galactopyranosyl-D-glucose;* 4-(β-D-galactosido)-D-glucose; milk sugar. $C_{12}H_{22}O_{11}$; mol wt 342.30. C 42.10%, H 6.48%, O 51.42%. Present in milk of mammals: human 6.7%; cow's 4.5%. Milk at body temp contains lactose as an equilibrium mixture of 2 parts of α-lactose and 3 parts of β-lactose. By-product of the cheese industry, produced from whey: Davis, *Can. Dairy and Ice Cream J.* **19**, 52 (1940); *Milk Trade Gaz.* **12**, 4 (1941); F. Ullmann, *Encyklopädie der Technischen Chemie,* **VII**, 579 (2nd ed., 1931). Structure and configuration: Zemplén, *Ber.* **59**, 2402 (1926); Levene, Sobotka, *J. Biol. Chem.* **71**, 471 (1926); Levene, Wintersteiner, *ibid.* **75**, 315 (1927); Haworth, Long, *J. Chem. Soc.* **1927**, 544; Hudson, *J. Am. Chem. Soc.* **52**, 1712 (1930); Hassid, Ballou in *The Carbohydrates,* W. Pigman, Ed. (Academic Press, New York, 1957) p 495. Synthesis: Haskins *et al., J. Am. Chem. Soc.* **64**, 1852 (1942). *Reviews:* Whittier, *Chem. Rev.* **2**, 85-125 (1926); *J. Dairy Sci.* **27**, 505-537 (1944); Weisberg, *ibid.* **37**, 1106-1115 (1954); L. A. W. Thelwall, *Dev. Food Carbohyd.* **2**, 275-326 (1980).



α-Lactose monohydrate, is the usual milk sugar and the lactose of pharmacy. Monoclinic sphenoidal crystals from water. Faintly sweet taste. Stable in air, but readily absorbs odors. d^{20} 1.53. Becomes anhydrous at 120°. mp 201-202° (rapid heating). Shows mutarotation. $[\alpha]_D^{20}$ +92.6° → +83.5° (10 min.) → +69° (50 min) → +52.3° (22 hrs, c = 4.5). The final value is obtained instantly in the presence of a trace of NH_3. U.S.P. requires +52.2° to +52.5° (c = 10). One gram dissolves in 5 ml water, in 2.6 ml boiling water; very slightly sol in alcohol. Insol in chloroform, ether. Ka at 16.5° = 6.0×10^{-13}. d_4^{20} of aq solns calcd for the monohydrate: 5.2% = 1.018; 10.2% = 1.038; 20.0% = 1.078; 30.2% = 1.123; 50.9% = 1.226; 60.8% = 1.281; 69.1% = 1.330.

β-Lactose, $C_{12}H_{22}O_{11}$. Obtained by crystallizing concd solns of α-lactose above 93.5°. Somewhat sweeter than the α-form. $[\alpha]_D^{25}$ +34° (3 min) → +39° (6 min) → +46° (1 hr) → +52.3° (22 hrs). One gram dissolves in 2.2 ml water at 15°, in 1.1 ml boiling water. After a few days crystals of the less sol α-monohydrate appear from satd solns.

On hydrolysis with 2% H_2SO_4 or with emulsin lactose yields 1 mol D-glucose and 1 mol D-galactose. Reduces Fehling's soln.

USE: Both forms of lactose are employed, with the α-form predominating: as a nutrient in preparing modified milk and food for infants and convalescents (Whittier, "Lactose and Its Utilization," *loc. cit;* review with 327 ref). In baking mixtures. Pharmaceutic aid (tablet and capsule diluent). To produce lactic acid fermentation in ensilage and food products. As chromatographic adsorbent in analytical chemistry. In culture media. For many other uses see the comprehensive review by Weisberg "Recent Progress in the Manufacture and Use of Lactose," *loc. cit.*

THERAP CAT (VET): Added to cow's milk for feeding orphan foals.

5222. Lactucarium—"French". Thridace. Inspissated juice of *Lactuca sativa* L., var. *capitata* L., *Compositae. Constit.* Lactucin, hyoscyamine, mannite.

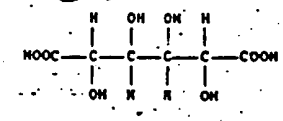
Brown pieces or powder; bitter taste; opium-like odor. Partly sol in water, alcohol, ether.

5223. Lactucarium—"German". "Lettuce opium". Dried milk-juice of *Lactuca virosa* L., *Compositae* (wild lettuce). *Constit.* About 0.2% lactucin; about 50% lactucerol; hyoscyamine, lactucic acid, caoutchouc, volatile oil, mannite.

Brown powder or irregular pieces; wax-like when cut; bitter taste. Partly sol in water, alcohol, ether. *Keep dry.*

THERAP CAT: Sedative.

5224. Lactucin. *3,3a,4,5,9a,9b-Hexahydro-4-hydroxy-9-(hydroxymethyl)-6-methyl-3-methyleneazuleno[4,5-b]furan-2,7-dione.* $C_{15}H_{16}O_5$; mol wt 276.30. C 65.21%, H 5.84%, O 28.95%. From various *Lactuca* spp and *Cichorium intybus* L., *Compositae.* Isoln: Schenck, Graf, *Arch. Pharm.* **274**, 537 (1936); **275**, 36 (1937); Schenck *et al., ibid.* **294**, 17 (1961). Purification: Späth *et al., Monatsh.* **82**, 114 (1951). Structure: Dolejs *et al., Coll. Czech. Chem. Commun.* **23**, 2195 (1958); Barton, Narayanan, *J. Chem. Soc.* **1958**, 963; Michl, Högenauer, *Monatsh.* **89**, 317 (1958). Revised stereochemistry: Bachelor, Itô, *Can. J. Chem.* **51**, 3626 (1973).

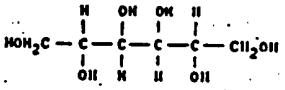


Cryst powder, dec about 255° when rapidly heated, also reported as 225°. Soluble in 300 parts cold water, 60 parts boiling water, alkalies; practically insol in alcohol, ether.

Ammonium salt, $(NH_4)_2C_6H_8O_7$, acicular crystals. Soluble in water.

USE: Has been proposed to replace potassium bitartrate in baking powder and for manuf of granular effervescing salts.

4238. Galactitol. Dulcitol; dulcite; dulcose; euonymit; melampyrite; melampyrum; melampyrin. $C_6H_{14}O_6$; mol wt 182.17. C 39.56%, H 7.75%, O 52.70%. Found in dulcite or Madagascar manna (*Melampyrum nemorosum* L.) and in other species of *Melampyrum, Scrophulariaceae,* and *Evonymus atropurpureus* Jacq., *Celastraceae.* Isoln: Hünefeld, *Ann.* 24, 241 (1837); Bouchardat, *Ann. Chim. Phys.* 27, 68 (1872); Fischer, Hertz, *Ber.* 25, 1261 (1892); Rogerson, *J. Chem. Soc.* 101, 1040 (1912). Prepn by catalytic isomerization of D-glucitol: Wright, Hartmann, *J. Org. Chem.* 26, 1588 (1961). Synthesis: Lespieau, *Bull. Soc. Chim. France* [5] 1, 1374 (1934); Delepine, Horeau, *ibid.* 4, 1524 (1937); Wiemann, Gordon, *ibid.* 1958, 433. Structure: R. L. Lohmar "The Polyols" in W. Pigman, *The Carbohydrates* (Academic Press, New York, 1957) p 247.

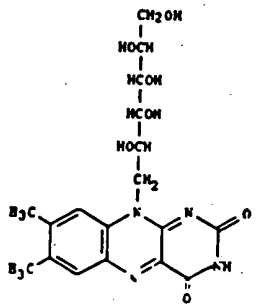


Crystals from methanol + water, mp 188-189°. Slightly sweet taste. d^{20} 1.47. bp_1 275-280°. One gram dissolves in 30 ml water, in 2 ml boiling water. Slightly sol in alc. Ka at 18° = 3.5×10^{-14}.

Hexa-*O*-acetylgalactitol, $C_{18}H_{26}O_{12}$, crystals from ethanol, mp 168-169°.

Hexanitrate, *nitrodulcitol,* mp 94-95°. Has explosive properties: Taylor, Rinkenbach, *J. Franklin Inst.* 204, 374 (1927).

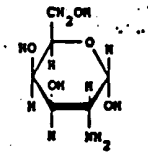
4239. Galactoflavin. *1-Deoxy-1-(3,4-dihydro-7,8-dimethyl-2,4-dioxobenzo[g]pteridin-10(2H)-yl)-D-galactitol; 7,8-dimethyl-10-(D-galacto-2,3,4,5,6-pentahydroxyhexyl)-benzo[g]pteridine-2,4(3H,10H)-dione; 7,8-dimethyl-10-(D-galacto-2,3,4,5,6-pentahydroxyhexyl)isoalloxazine;* 7,8-dimethyl-10-(*d*-1'-dulcityl)isoalloxazine; 6,7-dimethyl-9-(*d*-1'-dulcityl)isoalloxazine; 6,7-dimethyl-9-(1-deoxy-D-galactitol-1-yl)isoalloxazine. $C_{18}H_{22}N_4O_7$; mol wt 406.39. C 53.20%, H 5.46%, N 13.79%, O 27.56%. Prepd from 1-deoxy-1-(3,4-dimethyl-6-phenylazo)anilino-D-galactitol and barbituric acid: Berezovskii, Eremenko, *Zh. Obshch. Khim.* 32, 4056 (1962); *C.A.* 59, 736b (1963). Structure: Emerson *et al., J. Biol. Chem.* 160, 165 (1945). Pharmacology: Lane, Brindley, *Proc. Soc. Exp. Biol. Med.* 116, 57 (1964). Produces congenital malformations in animals: Nelson *et al., J. Nutr.* 58, 125 (1956); Miller *et al., J. Biol. Chem.* 237, 968 (1962); Mackler, *Pediatrics* 43, 915 (1969).



Yellow crystals, dec 260°. Absorption max: 223, 267, 370, 445 nm (ε 2730, 28100, 9100, 10800). Compd has yellow-green fluorescence in water.

USE: Riboflavine antagonist.

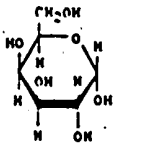
4240. D-Galactosamine. *2-Amino-2-deoxy-D-galactose;* chondrosamine; GalN. $C_6H_{13}NO_5$; mol wt 179.17. C 40.22%, H 7.31%, N 7.82%, O 44.65%. Amino sugar isolated from chondroitin sulfate, q.v.: P. A. Levene, F. B. La Forge, *J. Biol. Chem.* 18, 123 (1914). Sepn of α- and β-anomers: P. A. Levene, *ibid.* 57, 337 (1923). Synthesis: S. P. James *et al., Nature* 156, 308 (1945); *eidem, J. Chem. Soc.* 1946, 625; R. Kuhn, W. Kirschenlohr, *Ann.* 600, 126 (1956); P. A. Gent *et al., J. Chem. Soc. Perkin Trans. 1* 1972, 277. Chemistry: D. Horton in *The Amino Sugars* Vol. 1A, R. W. Jeanloz, Ed. (Academic, New York, 1969) pp 133-145. Inducer of exptl hepatitis: D. Keppler *et al., Exp. Mol. Pathol.* 9, 279 (1968); K. Decker, D. Keppler in *Progress in Liver Diseases* Vol. IV, H. Popper, F. Schaffner, Eds. (Grune & Stratton, New York, 1972) p 183. Powerful inhibitor of hepatic RNA synthesis: D. Keppler *et al., J. Biol. Chem.* 249, 211 (1974); T. Anukarahanonta *et al., Eur. J. Cancer* 16, 1171 (1980).



α-form

Hydrochloride, $C_6H_{14}ClNO_5$, crystals, mp 180° (dec). Shows mutarotation. α-Form: $[\alpha]_D^{25}$ +124° → +93° (water). β-Form: $[\alpha]_D^{25}$ +47° → 93° (water).

4241. Galactose. Cerebrose; brain sugar. $C_6H_{12}O_6$; mol wt 180.16. C 40.00%, H 6.72%, O 53.29%. Constituent of many oligo- and polysaccharides occurring in pectins, gums, and mucilages. Prepn: Kent, Tollens, *Ann.* 227, 224 (1885); E. P. Clark, *J. Biol. Chem.* 47, 2 (1921). Mutarotation and purification of β-form: C. S. Hudson, E. Yanosky, *J. Am. Chem. Soc.* 39, 1021 (1917). Structural configuration: J. Pryde, *J. Chem. Soc.* 123, 1809 (1923); W. Charlton *et al., ibid.* 1926, 94; W. N. Haworth *et al., ibid.* 1927, 2428; E. L. Jackson, C. S. Hudson, *J. Am. Chem. Soc.* 59, 994 (1937); R. M. Hann *et al., ibid.* 66, 1912 (1944). Isoln in the processing of the red alga, *Porphyra umbilicalis:* S. Peat *et al., J. Chem. Soc.* 1961, 1590. *Review:* W. Pigman, *The Carbohydrates* (Academic Press, New York, 1957) pp 88-90. Review of diagnostic use: W. J. Schirmer *et al., J. Surg. Res.* 41, 543 (1986).



α-D-galactose

α-Form, prisms from water or ethanol, mp 167°. $[\alpha]_D$ +150.7° → +80.2° (water). Soluble in about 0.5 parts water; freely sol in hot water; final soly in water at 25° = 68%; sol in pyridine; slightly sol in alcohol.

β-Form, crystals, mp 167°. $[\alpha]_D$ +52.8° → +80.2° (water). Sol in 1.7 parts water at 17°.

Monohydrate, prisms from water, mp 118-120°.

THERAP CAT: Diagnostic aid (hepatic function).

4242. D-Galacturonic Acid. $C_6H_{10}O_7$; mol wt 194.14. C 37.12%, H 5.19%, O 57.69%. Obtained by hydrolysis of pectin where it is present as polygalacturonic acid: Ehrlich, *Chem. Ztg.* 41, 197 (1917); Ehrlich, Guttmann, *Biochem. Z.* 259, 100 (1933); *Ber.* 66, 220 (1933); Niemann, Link, *J. Biol. Chem.* 95, 203 (1932); 104, 743 (1934); Morell, Link, *ibid.* 100, 385 (1933); Anderson, King, *J. Chem. Soc.* 1961, 5333.

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